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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 10 (24): 4461-4466, 2007
ISSN 1028-8880

Seroepidemiologic Study of Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus and Syphilis Infections in Iranian Blood Donors

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Abstract: To determine the frequency of hepatitis B, hepatitis C, Human Immunodeficiency Virus (HIV) and syphilis infections in Iranian blood donors. The prevalence of serological markers of hepatitis B, hepatitis C, HIV and syphilis infections were evaluated in 318029 consecutive volunteer blood donors attending to Tehran blood transfusion service from March 2005 to March 2006. Those positive for hepatitis B surface antigen, anti-HCV, anti-HIV1/2 and VDRL (venereal disease research laboratory) reactivity were analyzed with a second independent HBsAg enzyme immunoassay (EIA) and neutralization assay; an additional independent anti-HCV EIA and HCV-RIBA assay; second independent anti-HIV1/2 test, HIV western blot and fluorescent Treponemal Antibody Absorbed (FTA-ABS), respectively. In 318029 participants, prevalence of positive HBsAg, HCV RNA, HIV western blot and FTA-ABS was 1684 (0.487%), 323 (0.093%), 11 (0.003%) and 19 (0.005%), respectively. In 1014 subjects randomly selected from these 318029 participants, besides standard interview, physical exam and routine serologic tests; anthropometric and biochemical were studies. In this selected group frequency of HBsAg was 3 (0.29, 95% CI: 0-0.64%); frequency of anti-HCV was 21 (2.07%), but it was (0.09%, 95% CI: 0-0.30%) by confirmatory HCV RNA test; frequency of HIV-Ab1, 2 was 8 (0.78%), but it was 2 (0.19%, 95% CI: 0-0.48%) by confirmatory test; frequency of RPR was 0 (0%, 95% CI: 0-0.30%). Despite excluding subjects with high-risk behaviors by standard interview and physical examination, still a few asymptomatic hepatitis B, hepatitis C, HIV-infected subjects existed among volunteer blood donors with demographic and biochemical findings similar to non-infected ones.

Key words: Prevalence, serodiagnosis, hepatitis B, hepatitis C, HIV, syphilis, blood donors

INTRODUCTION

About more than 350 million HBsAg carriers in the world constitute the main reservoir of hepatitis B in human beings. Other groups with high rates of Hepatitis B Virus (HBV) infection include spouses of acutely infected persons, sexually promiscuous persons, health care workers exposed to blood, persons who require repeated transfusions especially with pooled blood product concentrates, residents and staff of custodial institutions for the mentally retarded persons, prisoners and, to a lesser extent, family members of chronically infected patients. Around 80% of HBV carriers reside in Asia.

In addition, 150 million people are infected worldwide with Hepatitis C Virus (HCV) (Keyvani *et al*., 2007). Hepatitis C can be transmitted by transfusion and percutaneous routes, such as self-injection of intravenous drugs. HIV is transmitted by both homosexual and heterosexual contact; by blood and blood products and by infected mothers to infants during pregnancy, delivery or via breast milk. This is an important form of transmission of HIV infection in developing countries, where the proportion of infected women to infected men is approximately 1:1. The current estimate of the number of cases of HIV infection among adults worldwide is approximately 33 million, two thirds of whom are in sub-Saharan Africa; 47% of cases are women (French, 2007).

Since little is known about the prevalence of viral hepatitis and HIV in Iranian Blood donors, we investigated in a great sample of Iranian patients (Alavian *et al*., 2002; Ansar and Kooloobandi, 2002; Ghavanini and Sabri, 2000). The aim of this cross-sectional study was to determine the prevalence of hepatitis B,

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hepatitis C, HIV and syphilis infections in 318029 Iranian voluntary blood donors and to see anthropometric and biochemical characteristics in 1014 participants of this group from March 2005 to March 2006.

MATERIALS AND METHODS

Clinical and laboratory assessment: All Iranian blood transfusion services, which referred to central branch of Tehran blood transfusion service from March 2005 to March 2006, perform an interview and clinical examination before sampling and high-risk groups including: persons with history of jaundice, intravenous drug abuse and high-risk sexual behavior were excluded, so the major bulk of positive cases would be cleared from the sampling. Blood donors were screened by history for high risk behaviors (unprotected sexual intercourse with multiple partners, intravenous drug use), travel history (to areas endemic for malaria), past and present illnesses and drug usage. After donor screening, blood was collected and tested for syphilis, hepatitis B, hepatitis C and HIV infection. Blood donors were notified of their test results privately and in the case of viral infectivity, their permanent deferral from donation is recommended and the donor is referred to a physician in special clinics in blood transfusion service for further evaluation (Alter *et al*., 1975).

All donations were tested for hepatitis B surface antigen, anti-HCV and anti-HIV1/2 and syphilis. Samples repeatedly reactive or indeterminate for HBsAg were further analyzed with a second independent HBsAg EIA and if further reactive, tested by a neutralization assay. All reactive samples were verified in a recognized confirmatory test (Enzygnost ® HBsAg 5.0, Enzygnost are registered trademarks of Dade Behring Marburg GmbH in the USA, Germany and other countries. Dade Behring Inc. New Yark, DE 19714 USA). Samples repeatedly reactive or indeterminate for anti-HCV were confirmed with an additional independent anti-HCV EIA and with a HCV-RIBA assay. Anti-HCV was tested by EIA (Avicenna kit-3rd generation, Cat. No. 02 EM 93-2, Avicenna Medical Center). Anti-HCV-EIA-Avicenna kit is a qualitative enzyme immunoassay for the detection of antibodies to hepatitis C virus (anti-HCV) in human serum or plasma and confirmed by HCV RIBA 3.0 (Genelab HCV RIBA 3). Samples repeatedly reactive or indeterminate for HIV were confirmed with a second independent anti-HIV1/2 test and a HIV western blot. Anti HIV-1/2 EIA and Western Blot confirmation was tested by (HIV Blot Genelab). For syphilis infection, RPR was tested by Enison kit. When the initial test result was reactive based on a treponemal assay, the donor was tested using a confirmatory treponemal-based assay, such as an FTA-ABS test. GGT and AST, ALT was measured by Pars Azmoon and Chimi Azmoon kits, respectively. The study proposal was approved by the ethics committees of Baqiyatallah University of medical sciences and blood transfusion service and a written informed consent was obtained from each participant.

In 318029 seemingly healthy Iranian subjects aged 18 to 68 years who attended to Tehran blood transfusion center for blood donation from March 2005 to March 2006, standard interview, physical exam and the above mentioned serologic tests, 1014 out of theses 318029 participants were randomly selected and enrolled in a cross-sectional study for anthropometric and biochemical evaluations: aspartate aminotransferase (AST), alanine aminotransferase, (ALT) and gamma glutamyltransferase (GGT) was measured. Moreover, personal history of diabetes mellitus and family history of chronic liver disease were recorded according to diagnosis of physician. Demographic findings such as Body Mass Index (BMI) as weight in kilograms/height in square meters, waist circumference, waist-hip ratio (WHR) as waist circumference at umbilicus/hip circumference at the maximal circumference over the buttocks were also recorded. Ever smokers defined as former and present smokers. Alcohol intake was assessed by history of alcohol consumption.

Statistical analysis: Quantitative variables were showed by mean±SD and qualitative variables were showed by number and percent. Ninety five percent confidence interval for prevalence was calculated by $P = p \pm 2 (pq/n)^{1/2}$; when we had no outcome and prevalence equalled zero, upper limit of prevalence was calculated by role of 3/n. Analysis was performed by SPSS software version 13.0 and p-value of less than 0.05 was regarded as significant.

RESULTS

In 318029 participants, prevalence of confirmed HBsAg, HCV RNA, HIV western blot and FTA-ABS positive was 1684 (0.487%), 323 (0.093%), 11 (0.003%) and 19 (0.005%), respectively. The mean age of 1014 subjects of this group was 40.94±11.09 years; range of age was 18 to 68 years. 957 (94.4%) were male and 57 (5.6%) were female. Mean AST level was 25.02±12.26 U L^{-1}, mean ALT level was 32.52±22.51 U L^{-1} and mean GGT was 24.87±18.59 U L^{-1}. Family history of liver disease, personal history of alcohol consumption in recent 6 months and habit of cigarette smoking were positive in 2 (1.13%), 95 (9.3%) and 209 (20.6%) subjects,

Table 1: Demographic and biochemical findings of 1014 subjects randomly selected from 318029 studied participants

Parameters	Positive (n = 4)	HBsAg negative (n = 992)	p-value*	Positive (n = 2)	HCVAb negative (n = 944)	p-value*	Positive (n = 5)	HIVAb negative (n = 941)	p-value*
Sex									
• Male	3	953	0.2	2	954	0.8	5	951	0.5
• Female	1	56		0	57		0	57	
OR (95% CI)¥	0.1 (0.01-1.7)			-			-		
Age	48.50±19.5	40.93±11.1	0.177	46.50±14	40.90±11	0.484	40.00±2.8	40.90±11.2	0.497
Weight	79.25±12.2	82.40±14.7	0.669	84.50±6.3	82.38±14	0.720	82.20±6.5	82.39±14	0.952
Height	166.52±7	173.58±15.6	0.137	172.50±3.5	173.56±15	0.744	173.60±5.8	173.56±15	0.989
Waist circumference (cm)	87.50±9.9	95.37±10.4	0.1	87.00±4.2	95.36±10.4	0.216	93.60±9.2	95.35±10.4	0.693
Hip circumference (cm)	102±6.7	101.60±10	0.8	94.50±3.5	101.70±10.4	0.207	102.60±10.1	101.68±10.4	0.845
Blood pressure (mmHg)	286.1±54	133.89±37	0.03	110.75±14	144.80±511	0.09	123.78±12	144.8±512	0.2
RH									
• Positive	3	906	0.3	2	907	0.7	5	904	0.5
• Negative	1	99		0	100		0	100	
OR (95% CI)¥	0.3 (0.03-3.1)			-			-		
AST	26.75±8.8	25.04±12.2	0.726	28.5±7.7	25.04±12.2	0.643	30.8±10	25.02±12.2	0.293
ALT	24.25±17.6	32.56±22.5	0.417	37.5±13	32.51±22	0.692	46.2±23	32.45±22	0.174
GGT	18.50±14.3	24.87±18.6	0.440	22.0±18	24.85±18.5	0.862	23.2±18	24.86±18	0.842

*: p-value were calculated by Independent Samples Test for quantitative variable and Pearson Chi-square for categorical variables. ¥: Odds ratio (95% CI) was calculated by Mantel-Haenszel Common Odds Ratio Estimate

respectively. Frequency of HbsAg positive was 4 (0.29%) and frequency of hepatitis C virus antibody was 21 (2.07%), but by HCV RNA confirmatory test, it was 2 (0.19%); frequency of HIV-Ab 1, 2 was 8 (0.78%), but by confirmatory test it was 5 (0.39%); frequency of RPR was 0. One case of HCV infection was also HBsAg positive. All hepatitis and HIV infected blood donors were male without personal history of cigarette smoking or alcohol consumption and they were unaware of their infections. Also, neither of them had personal history of diabetes, nor family history of chronic liver disease. Comparing the demographic and biochemical findings of hepatitis B, C and HIV infected volunteer blood donors with those seronegative for hepatitis B, C and HIV infections, it was found that, they were similar ($p>0.05$) (Table 1).

DISCUSSION

Prevalence of hepatitis B, hepatitis C, HIV and syphilis is dependent on many factors, such as number of infected persons in the family, prevalence of infection in the area the subject lives, frequency of the disease in the neighboring countries and rate of immigration (Wang *et al*., 2004). Other known routes that may influence on prevalence of these infections are number of subjects on hemodialysis, or subjects with hemoglobinopathy and coagulopathy that need transfusion or regarded as a route of transmission, numbers of injection drug users and addicts, exposure by sex contact, level of performance of sanitary rules and disposable devices in clinics (Pereira, 2003).

In this study, the frequency of positive hepatitis C virus infection was 1 (0.09%). It seems that the whole population prevalence of hepatitis C is less than 1% in Iran (Alavian *et al*., 2002). Volunteer blood donors seem healthier than general population. Nevertheless, prevalence of hepatitis B, C infections in blood donors is still based on prevalence of infection in the population.

In a study (Ghavanini and Sabri, 2000), the prevalence rate of HBsAg and anti-HCV among 7897 healthy voluntary blood donors in Shiraz, south west of Iran, was 85 (1.07%) and 47 (0.59%), respectively. Prevalence of hepatitis C infection in healthy blood donors ranges from 0.01-0.02% in the northern Europe and 1-1.5% in southern Europe to 6.5% in parts of equatorial Africa (Wasley and Alter 2000). Prevalence rates as high as 20% have been found in Egypt (Habib *et al*., 2001). Recently, a study on 5976 blood donors in Rasht, north of Iran, showed that 0.5% of the cases were positive for HCV antibody (Ansar and Kooloobandi, 2002). Others, on north west, reported a prevalence of 0.97% positive HCV Antibody (Alizadeh *et al*., 2006). The main problem with all of these studies is probability of selection bias and low positive predictive value of routine HCV Ab, detection by enzyme-linked immunoassay (ELISA) tests in blood donors. All of Iranian blood donation clinics follow regulations of Iran's Blood Transfusion Organization (IBTO) that exclude high-risk groups i.e., persons with history of jaundice, intravenous drug abuse and high-risk sexual behavior, so the major bulk of positive cases are ruled out from the sampling; the exclusion rate reaches to 19.7% due to all causes in Tehran (Ghavanini and Sabri, 2000). Another study mentioned that with more restrict regulations in selecting Iranian blood donors, the prevalence of hepatitis C may decrease to 0.12% (Alavian *et al*., 2002).

The sensitivity and specificity of the currently available tests for anti-HCV are not well defined. Not all donors implicated in the transmission of hepatitis C are

anti-HCV positive. One study estimated the incidence of 1-4% post-transfusion hepatitis C per transfusion recipient and concluded that approximately 25% of patients with post-transfusion hepatitis C received units from donors who tested negative for anti-HCV by EIA (Alter *et al*., 1972). In two studies of randomly selected blood donors reactive for anti-HCV by EIA, only 19-26% were anti-HCV positive on supplemental testing (IB) and 20-24% were judged indeterminant (Menitove *et al*., 1990; Zuck *et al*., 1990). In both of these studies, EIA reactive donors who were positive by supplemental tests were more likely to have an elevated ALT level (or anti-HBc positivity) than EIA reactive donors who were negative by these supplemental tests. Serologic surveys in groups other than blood donors have found that supplemental tests are positive among 84% (by IB) of EIA-reactive samples from previous transfusion recipients (Zuck *et al*., 1990) and among 80% (by NT) of EIA-reactive samples from parenteral drug users.

According to the findings of de Santana *et al*. (2005), in 30232 volunteer blood donors from the main blood bank of the city of Salvador, Brazil, 528 (1.7%) were anti-HCV positive. In this study, liver injury severity was significant in patients with elevated ALT; however, many subjects with normal ALT levels also presented with chronic hepatitis and cirrhosis. Use of more accurate tests as Nucleic Acids Test (NAT) system screening whole blood donors for infections with Human Immunodeficiency Virus (HIV) and hepatitis C virus, reduction of window-period in HBV transmission through detection of HBV DNA-positive units by minipool nucleic acid testing (MP NAT) would be expected to decrease this risk (Kleinman *et al*., 2005). A combination of more sensitive third-generation tests such as reversed passive hemagglutination and radioimmunoassay (RIA) for HbsAg screening and exclusive use of non-paid donors reduced the rate of post-transfusion hepatitis B to 0.3-0.9% per transfusion recipient by the mid-1970s (Alter *et al*., 1972, 1975). Another study, recommended improvement of blood donor selection, using more sensitive testing protocols, regarding reasons for the persistence of a residual risk of infection transmission such as blood collected within the HBsAg-negative period of early infection, or existence of chronic carriers with either very low levels of HBsAg or mutant forms of HBV (Pereira, 2003). From approximately 1, 200, 000 portions of blood that were anti-HIV screened in Denmark, 19 donors were found to be anti-HIV positive (Schmidt and Dickmeiss, 1990). During the same period, 12 cases of transfusion-associated HIV infection were found at follow-up control of recipients of blood from previous donations by donors demonstrated to be positive after 1986. One case of HIV infection could be attributed to transfusion with screened anti-HIV negative blood. The risk that a screened anti-HIV negative blood portion in Denmark can transmit HIV infection was less than one per 400,000. A study (Claudon-Charpentier *et al*., 2000), in Zimbabwe, reported that the all inclusive HIV percentage in total blood donations was less than 2% from an upward trend which was exceeding 5% by 1989.

Intravenous drug addicts are a source of hepatitis B, C and HIV transmission to others. In a study in drug addicts of Zanjan, Iran (Mansour-Ghanaei *et al*., 2002), the prevalence of HIV infection was 1.2%, HBV infection 3.8% and HCV infection 47.4%. In another study of IV drug abusers (Calzavara *et al*., 2003), HCV antibody was positive in 182 from 402 cases (45.3%). It appears that HIV infection in our country is increasing rapidly. The most common route of infection in 2001 was IV drug abuse (64%) (Keyvani *et al*., 2007).

Studies in other countries have mentioned that, the increasing imprisonment rate of drug users was linked to a spread of infectious diseases in prisons (HIV and hepatitis B and C). Several studies indicate a close correlation of imprisonment and transmission of infectious diseases. Butler *et al*. (1997), suggested that about a third of adult male prisoners entering the New South Wales (NSW) correctional system might have been infected with HBV or HCV. The increased risk of HBV, HCV and HIV infection among IDU who had shared syringes in prison warrants specific preventive action (Stark *et al*., 1997). Calzavara *et al*. (2003) stated that the possibility of transmission of Human Immunodeficiency Virus (HIV), hepatitis C or other blood-borne diseases exists in Ontario correctional centers. In this setting, drug injection while incarcerated is primarily related to opiate use prior to incarceration.

Chironna *et al*. (2003) showed that only 10% of children aged up to 10 years and 2.8% of subjects aged 11-20 years had been vaccinated against HBV. This survey showed that HBV infection is endemic and there is a need for a universal immunization strategy for HBV in the Kurd population.

South East Asia is experiencing a severe shortage of safe blood. Use of professional blood sellers, replacement of blood by relatives of patients, lack of any national blood policy, routine testing the viruses B, C, HIV in blood screening is necessary. This study reported that in the screened blood in India, the seroprevalence of hepatitis B was 0.06-8.5% and that of hepatitis C was 1.2-3%. While in Islamabad, Pakistan, testing results

showed that 8.1% of blood was infected with hepatitis C. Lastly, 5-10% of HIV infections in Southeast Asia are transfusion-induced (Sharma 2000). While VDRL reactivity in blood donors reported from other countries (French, 2007) varies from 0.8% in voluntary donors to more than 15% in paid commercial donors, there was no syphilis infection in our study population. Selected permanent voluntary blood donors other than paid or replacement donation for relatives or friends is the reason of safe transfusion in case of syphilis infection in our country. Developed countries have come to demand absolute freedom from transfusion-transmitted infection; while simultaneously considering that zero-risk transfusion is unlikely to ever be achieved (Klein, 2001). It is better to reduce blood transfusion as little as possible in these patients.

Screening blood donors is cost-effective, since the probabilities of developing acute fulminant hepatitis or becoming chronic carrier may be higher among blood recipients. Vaccination against hepatitis B especially for permanent blood donors and post exposure prophylaxis for hepatitis, follow-up of patients who received transfusion and introducing infected cases to specific clinics for education them and their families for national health benefits is mandatory. Screening blood donors facilitate to diagnose previously unrecognized asymptomatic persons with established chronic hepatitis C that exist among blood donors (McLindon *et al*., 1995).

Noting particular epidemiology of disease transmission and subpopulations predisposed for infection, routine screening of infected ones and their families, funding for prevention, education, voluntary counseling, considering improved and additional harm reduction strategies, precautions emphasized in health care settings that provide health care and waste disposal, other main risk factors for infection transmission and drug assistance programs is demanded.

CONCLUSIONS

Risk of transmission of viral infection by transfusion of blood components, despite the improvement of donor selection and the continuous improvement of screening tests, remains. More specific and more sensitive methods of screening will reduce the transmission of these viruses in the population. Despite excluding subjects with high-risk behaviors by standard interview and physical examination, still a few asymptomatic hepatitis B, hepatitis C, HIV-infested subjects existed among volunteer blood donors with similar demographic and biochemical findings to non-infected ones.

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